

**REMARKS**

The applicants acknowledge that the Examiner has agreed to at least examine in one application a method of diagnosing a disease, comprising detecting a polypeptide tumor-associated antigen, wherein said antigen has a sequence encoded by the nucleic acid of SEQ ID NO: 7 or SEQ ID NO: 117.

The Examiner has stated his willingness to examine such method of diagnosing a disease insofar as it relates to a polypeptide of SEQ ID NO: 163 SEQ ID NO: 118 or a polypeptide encoded by a nucleic acid that hybridizes to a nucleic acid of SEQ ID NO: 7 or SEQ ID NO: 117 or a portion thereof.

Claims 99-104 and 107-115 are pending after entry of this paper. Claims 99-106 have been rejected. Claims 107-115 are withdrawn. Claims 1-98, and 105-106 are cancelled without prejudice. Applicants reserve the right to pursue withdrawn or cancelled claims in a divisional or continuing application. Claim 99-104 have been amended. No new matter has been introduced by these amendments. Support for the amendment can be found in the originally filed specification.

Reconsideration and withdrawal of the pending rejections in view of the above claim amendments and below remarks are respectfully requested.

**RESPONSE TO SPECIFICATION OBJECTIONS**

The Examiner has objected to the disclosure made in the application due to informalities in the abstract. Specifically, legal phraseology has been removed to address the Examiner's concern. Accordingly, the abstract has been amended and presented on a separate paper hereto.

The Examiner has objected to the arrangement of the specification. Specifically, the Examiner points to the allegedly missing Title of the Invention, Background of the Invention, and a Brief Summary of the Invention. The applicants respectfully direct the Examiner's attention to the title of the application as filed on page 1: "Genetic products differentially expressed in tumors and the use thereof". The title was provided in the originally filed application and should not be objected to.

Applicants point to the Guidelines that the Examiner has presented on page 6 of the Office Action which states that the “guidelines are suggested for the applicant’s use. “ These are not required headings. However, in order to expedite prosecution of the instant application, applicants have added the headings. Specifically, prior to paragraph [0001], the Background of the Invention” has been inserted, and the “Summary of the Invention” has been inserted before paragraph [0003].

The Examiner suggests that the figures should be labeled as “Brief Description of the Several Views of the Drawings”. The applicants have amended the specification by inserting the “Brief Description of the Several Views of the Drawings” prior to paragraph [0155] in accordance with the Examiner’s suggestion. Reconsideration and withdrawal of the specification objections are respectfully requested.

#### PRIORITY

The applicants provide herewith a translation of the German patent application DE10254601.0 to which the instant application claims priority. The German patent application has filing date of November 22, 2002. Accordingly, the applicants respectfully request the Examiner to correct the priority date of the instant application.

#### RESPONSE TO REJECTIONS UNDER 35 U.S.C. §112

Claim 103 has been rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. To address the Examiner’s concern and solely for expediting prosecution of the instant application, the applicants have amended claim 102 and replaced the phrase “in a detectable manner” with “with a detectable marker.” Support for the amendment can be found in paragraph [0043]. Applicants respectfully request reconsideration and withdrawal of the §112 rejection to claim 103 in view of the claim amendment.

Claim 106 has been rejected under 35 U.S.C. §112, first paragraph as failing to comply with the enablement requirement. The applicants have cancelled claim 106 to render this objection moot. Reconsideration and withdrawal of the §112 rejection to claim 106 is respectfully requested.

Claims 99-106 have been further rejected under 35 U.S.C. §112, first paragraph as allegedly failing to comply with the enablement requirement because the Examiner contends that the application does not disclose that the expression of the claudin-18A1 protein is activated in tumor cells compared to normal cells. The Examiner states that expression of claudin-18A1 mRNA may not necessarily correlate with expression of claudin-18A1 protein. To overcome the Examiner's objection, the applicants have amended claim 99 by removing reference to marker SEQ ID NO: 117 or 118 and the phrase "or a portion thereof" related to claudin-18A1. The support for these amendments can be found throughout the application. Reconsideration and withdrawal of the §112 rejections to claim 99-106 are respectfully requested.

Claims 99-106 have been further rejected under 35 U.S.C. §112, first paragraph as failing to comply with the enablement requirement because the Examiner alleges that that the instant application does not demonstrate activation of claudin-18A2 protein expression in any disease.

Applicants respectfully disagree. The applicants respectfully submit that the data related to bronchial carcinoma was disclosed for the purpose providing an example and that, with respect to other cancer types disclosed in the present specification, protein expression data correlate with expression of mRNA. As such, the present application demonstrates that claudin-18A2 mRNA as well as claudin-18A2 protein is aberrantly activated in pancreas carcinomas, esophagus carcinomas and bronchial carcinomas as described in Table 3A and paragraph [0305] of the published specification. However, for further clarification, the applicants have added the term "cancer" disease in claim 99. The applicants believe that specifying the disease to be diagnosed to specific cancer types would unduly limit the scope of the claims to the specific embodiments disclosed in the examples.

With respect to the Examiner request that the applicants clarify the meanings of the terms "bronchial carcinomas" and "lung tumors", the applicants respectfully point to the published specification at paragraph [0301], which states that bronchial carcinoma is a lung tumor, i.e. a particular lung tumor. Furthermore, the applicants respectfully point out that the terms "bronchial carcinoma" and "lung cancer" are used interchangeably in the art. Reconsideration and withdrawal of the §112 rejections to claims 99-106 are respectfully requested.

Claims 99-106 have been further rejected under 35 U.S.C. §112, first paragraph as lacking adequate written description in the specification. The Examiner alleges that the instant application concerns the detection of a portion of a claudin- 18 protein or a polypeptide encoded by a portion of a claudin- 18 nucleic acid, and therefore, it lacks an adequate written description. To address the Examiner's concern, the applicants have amended claims 99 and 100 to delete the term "portions thereof". Support for the amendment can be found throughout the application. Reconsideration and withdrawal of the §112 rejections to claims 99-106 are respectfully requested.

#### Response to Rejections under 35 U.S.C. §102

Claims 99-104 have been rejected under 35 U.S.C. §102(b) as being anticipated by Rosen et al. (WO 01/54708). In particular, the Examiner states that Rosen teaches the use of antibodies to claudin-18A2 for the diagnosis of lung, pancreatic and testicular cancer, where claudin-18A2 polypeptide expression is at a higher level in the diseased tissues than in the normal tissues.

The applicants respectfully disagree with the Examiner's rejections. The instant application discloses a method of diagnosing cancer by identifying increased levels of the tumor-associated antigen. Paragraph [0305], Example 4 and Table 3A of the instant application describe how the increased protein level of claudin-18A2 is measured using an antibody assay to diagnose cancer.

Contrary to the Examiner's contention, Rosen does not disclose any teachings as to claudin-18A2 protein expression. Rather, Rosen describes a method of diagnosis based on an analysis of the mRNA derived from various cell lines. Furthermore, the reference discloses that the claudin-18A2 gene is expressed primarily in adult and fetal lung tissue and to a lesser extent in pancreatic and testicular tumors (see page 9, lines 38-39). The expression data presented in Table 3 on page 81 of Rosen indicates that increased expression for cDNA clone HTPFX16, which appears to encode claudin-18A2, was observed in the following cDNA libraries:

H0024: Human fetal lung III

H0039: Human pancreas tumor, disease

H0040: Human testes tumor, disease

H0622: Human pancreas tumor, re-excision, disease

L 1290: Testis

S0434: Stomach normal, disease

The applicants respectfully direct the Examiner's attention to the contradictory cDNA expression data in stomach, S0434, where increased expression for cDNA for claudin-18A2 is observed both in normal and diseased state. Additionally, according to Rosen, no expression was found, in for example:

H0343: Stomach cancer (human), disease

H0595: Stomach cancer (human), re-excision, disease

Rosen does not disclose any data regarding an aberrant activation of claudin-18A2 protein in tumors. According to the Examiner in section 12 of the Office Action, mRNA expression data cannot be used to extrapolate to an aberrant expression of the protein encoded thereby. Since, the applicants believe that Rosen does not disclose an aberrant activation of claudin-18A2 protein expression in any cancer types since mRNA assays are performed, Rosen does not teach detecting the amount of claudin-18A2 protein expression in the diagnosis of cancer. Therefore, Rosen does not disclose the subject-matter of the claimed invention. Accordingly, reconsideration and withdrawal of the §102(b) rejection to claims 99-104 is respectfully requested.

Claims 99-104 have been further rejected under 35 U.S.C. §102(b) as being anticipated by Sheppard and Foley (WO 00/15659). In particular, the Examiner states that the reference teaches the use of antibodies to a polypeptide encoded by SEQ ID NO: 117 (i.e. claudin-18A1).

Applicants respectfully disagree. However, in order to expedite prosecution of the instant application, applicants have amended claim 99 by deleting the phrase "or 117 or a portion thereof". Support for the amendment can be found throughout the application. The applicants respectfully request reconsideration and withdrawal of the §102(b) rejection to claim 99.

Dependent Claims

The applicants have not independently addressed all of the rejections of the dependent claims. The applicants submit that for at least similar reasons as to why independent claim 99 from which all of the dependent claims 100-104 depend are believed allowable as discussed *supra*, the dependent claims are also allowable. The applicants however, reserve the right to address any individual rejections of the dependent claims and present independent bases for allowance for the dependent claims should such be necessary or appropriate.

Thus, applicants respectfully submit that the invention as recited in the claims as presented herein is allowable over the art of record, and respectfully request that the respective rejections be withdrawn.

**CONCLUSION**

Based on the foregoing amendments and remarks, Applicants respectfully request reconsideration and withdrawal of the rejection of claims and allowance of this application.

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**AUTHORIZATION**

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **13-4500**, Order No. 4883-0001.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **13-4500**, Order No. 4883-0001.

Respectfully submitted,  
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